

## Topic: Use of medications containing codeine and tramadol in children

Based on recommendations from the Illinois Drug Utilization Review Board, HFS is implementing an age edit that requires prior authorization for use of these products in children younger than 18 years of age effective **April 6, 2018**.

### Background

#### Codeine

Codeine alone or in combination with other medications is used to treat pain and cough. The prodrug codeine is metabolized via the hepatic cytochrome-p450 isoenzyme 2D6 (CYP2D6) to morphine. Genetic differences in CYP2D6 can lead to significantly varying morphine blood levels. In poor metabolizers codeine will not be converted to morphine, leading to lack of efficacy. Conversely, ultra-rapid or extensive metabolizers may cause codeine to be converted to morphine faster, resulting in toxicity. Morphine toxicity can occur after a single dose or 1-2 days after codeine is started (median 5 doses). Adverse effects can occur when blood levels are within the therapeutic range or increased. Genotyping is not conducted routinely prior to use due to cost.<sup>1</sup>

The Food and Drug Administration (FDA) review of Adverse Event Reporting System data for codeine-containing products identified 64 cases of severe respiratory depression resulting in 24 deaths and 21 hospitalizations. At least 78% of the events were in children younger than 12 years of age. At least 41% of 334 pediatric Emergency Room visits due to sedation and unusual sleepiness from codeine products occurred in children 12-18 years of age.<sup>1</sup> The FDA's public health advisories caution about variable codeine metabolism and risk of respiratory depression, even in breastfed infants of mothers taking codeine.<sup>2</sup> Drug Safety Communications warn about death and respiratory depression post-tonsillectomy or adenoidectomy to treat obstructive sleep apnea.<sup>3</sup> Boxed warnings address the contraindication for post-operative use of codeine in children, slowed or difficult breathing, and risks of misuse, abuse, addiction, overdose, and death.<sup>2,4</sup> **As of January 2018, FDA approved indications limit use of prescription cough and cold medicines that contain codeine or hydrocodone to adults 18 years of age and older.**<sup>4</sup>

#### Tramadol

Tramadol alone or in combination with acetaminophen is indicated for treatment of pain in adults. Tramadol is metabolized by hepatic CYP2D6 O-demethylation to the active metabolite, O-desmethyltramadol, and by CYP3A4 to an inactive metabolite. Ultra-rapid metabolizers convert tramadol more rapidly to the active metabolite, while poor metabolizers may accumulate tramadol. Tramadol metabolism may also be inhibited by other medications, resulting in accumulation.<sup>5</sup> The FDA identified cases of serious slowed or difficult breathing in children less than 17 years of age who received one or more doses of tramadol after tonsillectomy or adenoidectomy (off-label use).<sup>6</sup> Tramadol use in children is contraindicated and use is not recommended in breastfeeding women.<sup>2</sup>

### Treatment options

#### Pain

Acute mild pain in children should be treated first with hydration and acetaminophen or ibuprofen.<sup>1,5,7-10</sup> Potential adverse effects of ibuprofen on platelet function and post-operative bleeding are of limited concern post-tonsillectomy.<sup>10</sup> If moderate to severe pain cannot be controlled, a narcotic, such as low-dose morphine, may be used short term (3 days).<sup>1,7,9,11</sup> Adjuvant medications, such as anticonvulsants and antidepressants may be helpful depending on the condition being treated.<sup>7,9</sup> In the Emergency Room, after failure of ibuprofen and acetaminophen, oral oxycodone was previously recommended. Oxycodone also poses risks due to variable pharmacokinetics in children and increased toxicity in ultra-rapid metabolizers.<sup>5,8</sup> Topical anesthetics may be appropriate for some procedures. Oral sucrose is an option in neonates and infants younger than 6 months of age.<sup>8</sup> In children with severe neurological impairment, medications that address CNS sources of pain, such as gabapentin, may be preferred before 24-hour opioid therapy is used.<sup>9</sup> Children should not be given codeine or tramadol-containing products postoperatively.<sup>1,9</sup> Tramadol and codeine

are contraindicated in children less than 12 years of age. They should not be used in adolescents 12-18 years of age who are obese, have obstructive sleep apnea, or severe lung disease, which can increase risk of respiratory depression and death, particularly if they are ultrarapid metabolizers. These products should also not be used in breastfeeding women.<sup>2</sup> If no other options for an individual patient exist, codeine can be administered as-needed (not scheduled basis) every 6 hours for 3 days up to maximum daily dose of 240 mg.<sup>1</sup> Parents need to watch for unusual sleepiness, confusion, and difficulty or noisy breathing. If these symptoms occur, the product should be stopped and emergency care received.

### Cough

Cough due to upper respiratory infections is short-lived (5-7 days) and usually does not require therapy.<sup>4,12-13</sup> Narcotics and dextromethorphan as antitussives are not recommended because they have not shown efficacy in lessening severity or duration of cough and these medications have safety risks.<sup>4,5,13</sup> Codeine or hydrocodone antitussives are now only indicated in adults 18 years of age and older.<sup>2</sup> The preferred treatment for children 1 to 18 years of age with cough due to common cold is honey. Honey has provided more relief than no treatment and diphenhydramine and is comparable to dextromethorphan. Honey should not be used in children < 1 year of age. Significant cough reduction has not been demonstrated with OTC antitussives, expectorants, mucolytic agents, antihistamine, or combination products.<sup>13</sup> If honey is not effective for children 2 years of age and older and parents insist on an OTC product, dextromethorphan and menthol lozenges or ointments have been used. In children 6 years of age or older, diphenhydramine, which can be sedating, can be tried. Diphenhydramine may cause paradoxical excitement in younger children. Children 10 years of age who can swallow oral medications can be prescribed benzonatate. Prior authorization may be required.

### **Next steps**

Codeine- or tramadol-containing medications for children < 18 years of age will require prior approval. If your pediatric patient has been filling these medications monthly for pain management, in the next few weeks, you will receive a pain management form. You will be asked to provide clinical data to help determine if chronic opioid therapy is appropriate. Please respond as soon as possible with requests for information to facilitate uninterrupted pain management as appropriate. If necessary, we will work with you to convert your patient to preferred short-acting narcotics for children or to taper the patient off opioid therapy. If your patients are being treated for pain due to cancer or sickle cell disease per HFS medical claim review, you will not receive a pain form.

### **References:**

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